REMARKS

Claims 1-64 are pending in the application and Claims 1-23, 26, 44-50, and 61-64 are currently under examination on their merits. Claims 1-8, 12, 17, 21-23, 26, 44, 45, 50, 61, 63, and 64 are being amended, as shown above. Entry of the proposed amendments is respectfully requested.

Where appropriate, Applicants have amended the claims to include limitations requiring that: (a) the two proteins of the claimed protein complex interact, (b) the GAG protein, fragment or homologue contain a late domain, and (c) the Tsg101 protein, fragment or homologue interacts with the GAG protein, fragment or homologue through this late domain. Also where appropriate, and for the purpose of consistency, claims have been amended to uniformly recite "Tsg101," "HIV GAG," and "HIV GAGp6" in lieu of "Tsg101 protein," "HIV GAG polypeptide," and "HIV GAGp6 protein," respectively. Finally, in some cases the claims are being amended to correct typographic errors not related to patentability. Applicants respectfully submit that the proposed amendments substantially improve the readability of the claims, and make the claims in condition for allowance or appeal.

In accordance with 37 C.F.R. 1.121(f), Applicants submit that none of these requested amendments adds new matter to the Application.

Election/Restriction:

Applicants requested in their response to the first Office Action on the Merits that Claim 26 be examined along with all other Claims in Claim Group I, on the grounds that the amended Claim 26 (presented in the Applicants' response to the Restriction Requirement) is drawn to a protein complex that is substantially identical to the protein complex of Claim 1. However, Claim 26 was inadvertently left out of Applicants' response to the First Office Action on the Merits. As encouraged by the Examiner, an amended Claim 26 has been reintroduced into the listing of the Claims (above). Applicants respectfully request that amended Claim 26 be considered by the Examiner.

Claim Rejections under 35 USC § 112, second paragraph

Claims 1-23, 44-50, and 61-64 stand rejected under 35 USC § 112, second paragraph, for allegedly being indefinite and failing to particularly point out and distinctly claim the subject matter which Applicants regards as his invention.

The Meaning of Certain Claim Terms Raised in Office Action: "Tsg101," "HIV GAG," and "HIV Gagp6"

To begin, it is noted that the Office Action states that the terms "Tsg101" and "HIV GAG polypeptide" are not defined.

Applicants note that the specification explicitly defines "Tsg101" to mean human Tsg101 protein. *See* Originally Submitted Specification, page 14, first paragraph. The amino acid sequence of human Tsg101 protein was generally known in the art at the time of filing. Further, the specification provides the GenBank Accession number for human Tsg101. *See* Originally Submitted Specification, Table 1, page 14. Moreover, the specification discusses extensively the prior art background on Tsg101. *See* Originally Submitted Specification, section 2.2, pages 33-34. Thus, Applicants respectfully submit that an ordinarily skilled person in the art would understand the meaning of the claim term "Tsg101" in view of the specification disclosures.

For purpose of consistency, all relevant claims have been amended to recite "Tsg101," "HIV GAG," and "HIV GAGp6" in lieu of "Tsg101 protein," "HIV GAG polypeptide," and "HIV GAGp6 protein," respectively.

With regard to "HIV GAG", it has been generally known in the art that the HIV *gag* gene is transcribed and translated into GAG (p55). GAG (p55) is a polyprotein, which is cleaved by HIV proteases into a set of mature proteins: HIV matrix protein (MA; p17), capsid protein (CA; p24), nucleocapsid proteins (NC, p7), and GAGp6. Indeed, the term "HIV GAG" is frequently referred to in scientific publications with a commonly understood connotation, i.e., the HIV GAG full-length protein, as opposed to the mature proteins. It is also noted that in Table 1 on page 14 of the Originally Submitted Specification, "HIV GAG" is indicated as a "protein," with its amino acid sequence provided by a reference to GenBank Accession No. AF324493. Thus, the

meaning of the term "HIV GAG" would be apparent to an ordinarily skilled person in the art of molecular biology in view of the disclosure in the specification.

With regard to HIV Gagp6, it is noted that the specification defines "HIV Gagp6" to mean HIV Gagp6 protein. *See* Originally Submitted Specification, page 14, first paragraph. The amino acid sequence of HIV Gagp6 is generally known in the art.

In view of the above explanation, Applicants trust that the meaning of terms "Tsg101," "HIV GAG," and "HIV Gagp6" should be amply clear to the Examiner, and to an ordinarily skilled person in the art of virology or molecular biology.

"UEV Domain"

The Office Action also asserts that the meaning of "UEV domain" is unclear. Applicants note that the as-filed specification defines the phrase "domain" as "a functional portion, segment or region of a protein, or polypeptide," on page 10. In addition, the as-filed specification states on page 33 that:

> "Tsg101 contains a ubiquitin-conjugating enzyme E2 catalytic domain. Recently, interest has focused on Tsg101 as a possible component of the ubiquitin/proteasome degradation pathway. By database search and comparison, it has been found that that N-terminal Tsg101 contains a domain related to E2 ubiquitin-conjugating (Ubc) enzymes although lacking the active site cysteine. *See* Koonin and Abagyan, *Nat. Genet.*, 16(4):330-1 (1997). Thus, Tsg101 may belong to a group of apparently inactive homologs of Ubc enzymes. *See id.* The domain related to E2 ubiquitin-conjugating (Ubc) enzymes is referred to ubiquitin E2 variant (UEV) domain."

Applicants note that the above referenced publication by Koonin and Abajyan (which is being supplied as **Exhibit A**) provides a multiple amino acid sequence alignment in which the N-terminal portion of human Tsg101 is aligned with other representatives of ubiquitin-conjugating (E2) enzymes. Therefore, the UEV domain is encompassed within the aligned region. Applicants respectfully submit that evidence that the metes and bounds of the term "UEV domain" were known to those of ordinary skill in the art at the time the instant application was filed is provided in a publication by VerPlank and colleagues (VerPlank *et al., Proc. Natl. Acad. Sci. U.S.A.* 98(14):7724-7729 (2001)), which was cited as publication B34 in the IDS submitted to the USPTO on

February 1, 2002. Specifically, VerPlank *et al.* state in the second paragraph in the right column of page 7727: "The Tsg101 protein contains an N-terminal E2-like (UEV) domain with homology to the Ub-conjugating (Ubc) 4 subgroup of E2 enzymes." Thus, read in the light of the specification, those skilled in the art would clearly understand the meaning of the term "Tsg101 UEV domain," and the rejection in this regard under 35 USC §112, 2nd paragraph should be withdrawn.

"Homologue" and "Fragment"

The instant Office Action also states that "the metes and bounds of the terms "homologue", and "fragment" are not clear." The claims have been amended, and in all claims that are pending now, the terms "homologue" and "fragment" are indicated with a functional limitation, i.e., as being "capable of interacting with" either HIV Gagp6 late domain or Tsg101. In addition, in the case of a "homologue" or "fragment" based on GAG or Gagp6, the claims have been modified to include structural features by indicating that such a homologue or fragment contains an HIV GAG late domain motif. Further, in the case of a "homologue," invariably the claims also define the homologue based on a percentage identity to a known protein or a functionally defined fragment that is readily obtainable to an ordinarily skilled person in the art.

For example, in the context of "HIV GAG fragment," the claims now recite "an HIV GAG fragment containing an HIV GAGp6 late domain motif and capable of interacting with Tsg101." As discussed above, the term "HIV GAG" is amply clear to an ordinarily skilled artisan. Applicants also note that the term "protein fragment" is defined on page 9 of the as-filed specification to mean: "a polypeptide that represents a portion of a protein", adding that "[w]hen a protein fragment exhibits interactions with another protein or protein fragment, the two entities are said to interact through interaction domains that are contained within the entities." *See* Originally Submitted Specification, page 9. Further, the term "HIV GAGp6 late domain" is a commonly used term in the field of virology, particularly among scientists studying viral budding. Besides, the explicit discussions and the context in the as-filed specification should make the term amply clear. *See* Originally Submitted Specification, bottom of page 33 to page 34.

The functional limitation "capable of interacting with Tsg101" further defines the "HIV GAG fragment" and makes clear that the fragment must be able to interact with Tsg101. Applicants note that

> "[a] functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. A functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step."

See MPEP 2173.05(g); Ori. 8th Ed., Rev. 1, Feb. 2003, pg 2100-206. Indisputably, at the time of filing of the application, an ordinarily skilled person in the art of molecular biology apprised of the as-filed disclosure would clearly understand the meaning of "an HIV GAG fragment containing an HIV GAGp6 late domain motif and capable of interacting with Tsg101." Besides, the specification provides specific and detailed teachings on how to make such a fragment. *See* Originally Submitted Specification, pages 45-46. Further, the specification teaches methods that can be used to determine whether such a fragment interacts with Tsg101. For example, on page 10, first full paragraph, the originally specification discloses a number of methods for determining an interaction between two proteins or protein fragments, including the yeast two-hybrid system. The yeast two-hybrid system is described in extensive details on pages 61-75 of the originally submitted specification, and in Example 1 (see pages 79-80). Other types of assays useful in determining whether a fragment interacts with a native protein are also taught in detail in the specification. *See* Originally Submitted Specification, Example 4 on pages 83-84, and pages 58-61.

Thus, Applicants respectfully submit that, apprised of the as-filed specification, the metes and bounds of the claim element "an HIV GAG fragment containing an HIV GAGp6 late domain motif and capable of interacting with Tsg101" is unambiguously defined, and the claims are clear and definite in this respect.

Similarly, in the context of "HIV GAG homologue," the claims now recite "a homologue of HIV GAG that is capable of interacting with Tsg101, has an amino acid sequence that is at least about 50% identical to that of HIV GAG and contains an HIV GAGp6 late domain motif."

As discussed above, the term "HIV GAG" is amply clear to an ordinarily skilled artisan, and its amino acid sequence is known in the art and provided in Table 1 by a reference to a specific GenBank Accession number. Applicants note that the term "homologue" is defined in detail in the as-filed specification. In particular, the term "homologue," when used in connection with a first native protein or fragment thereof that is discovered, according to the present invention, to interact with a second native protein or fragment thereof, is defined as:

> "[A] polypeptide that exhibits an amino acid sequence homology and/or structural resemblance to the first native interacting protein, or to one of the interacting domains of the first native protein **such that it is capable of interacting with the second native protein**" (emphasis added).

See Originally Submitted Specification, page 11, last paragraph to page 12, first paragraph. The as-filed specification further notes that "homologues may be the ortholog proteins of other species including animals, plants, yeast, bacteria, and the like" or, alternatively: "[h]omologues may also be selected by, e.g., mutagenesis in a native protein," and that a "homologue of a native protein may have an amino acid sequence that is at least 50%, preferably at least 75%, more preferably at least 80%, ... identical to the native protein." *See* Originally Submitted Specification, page 11, last paragraph to page 12, first paragraph.

Additionally, the specification provides specific and detailed teachings on how to make such homologues, e.g., by mutagenesis in a native protein. *See* Originally Submitted Specification, pages 12, 45-46. Further, the specification teaches methods that can be used to determine whether such homologues interact with Tsg101. For example, on page 12, first paragraph, the specification states that "[h]omologues may be identified by site-specific mutagenesis in combination with assays for detecting protein-protein interactions, e.g., the yeast two-hybrid system described below, as will be apparent to skilled artisans apprised of the present invention." *See* Originally Submitted Specification, page 12. The yeast two-hybrid system is described in extensive details on pages 61-75 of the originally submitted specification, and in Example 1 (see pages 79-80). Other types of assays useful in determining whether a homologue or a fragment interacts with a native protein are also taught in detail in the specification. *See* Originally Submitted Specification, Example 4 on pages 83-84, and pages 58-61.

Thus, Applicants respectfully submit that at the time of filing of the application, an ordinarily skilled person in the art of molecular biology apprised of the as-filed disclosure would understand the meaning of such a homologue of HIV GAG that is capable of interacting with Tsg101, has an amino acid sequence that is at least about 50% identical to that of HIV GAG and contains an HIV GAGp6 late domain motif.

Likewise, for the same reasons, the meaning of the amended claim terms "a Tsg101 fragment capable of interacting with HIV GAGp6 late domain" and "a homologue of Tsg101 capable of interacting with HIV GAGp6 late domain and having an amino acid sequence that is at least about 50% identical to Tsg101" are also clear to an ordinarily skilled person in the art of molecular biology.

It is true that the use of terms like "fragment" and "homologue" considerably broaden the scope of the claims of the instant application. However, "[b]readth of a claim is not to be equated with indefiniteness." *In re Miller*, 441 F.2d 680, 169 USPQ 597 (CCPA 1971); *MPEP* 2173.04; Ori. 8th Ed., Rev. 1, Feb. 2003, pg 2100-200. In view of the functional limitations and other claim amendments, and the teachings of the specification, these terms have definite meanings within the scope of the amended claims. Accordingly, Applicants believe that the amendments should fully address the Examiner's concerns. Withdrawal of the rejections under §112, 2nd paragraph is respectfully requested.

Claim Rejections under 35 USC § 102(b):

Claims 1-8, 12-15, 17-20, and 22 stand rejected under 35 USC § 102(b) as being anticipated by Ott *et al., J. Virol.* 72(4):2962-2968 (1998) (hereinafter "Ott"), or, in the alternative, under 35 USC § 103(a), for allegedly being obvious over Ott. To sustain a rejection under 35 USC § 102(b) or 35 USC § 103(a), the cited reference(s) must teach all the limitations of the claimed invention. Applicants respectfully submit that the cited reference does not provide all the limitations of the claims at issue.

Specifically, the Office Action asserts that Ott teaches that ubiquitin interacts with HIV GAGp6 and that ubiquitin "contains several short fragments that are over 4 residues long that are 100% identical to Tsg101 and binding can be based on those fragments."

Applicants note that the claims as amended now recite, in relevant aspects, "a homologue of said Tsg101 fragment capable of interacting with HIV GAGp6 late domain and having an amino acid sequence that is at least about 50% identical to said Tsg101 fragment."

Thus, the claims require that the homologue interact with HIV GAGp6 late domain. Even assuming ubiquitin is a homologue of Tsg101, Ott does not teach or suggest that ubiquitin interacts with HIV GAGp6 late domain. Rather, Ott teaches that ubiquitin is "covalently attached to internal lysines in a wide range of cellular proteins." *See* Ott at page 2962, bottom of left column (emphasis added). As is generally known in the art, ubiquitin's covalent attachment to lysines in proteins is catalyzed by ubiquitinating enzymes, in most cases one of many E2 enzymes. *See* Ott at page 2966, bottom of right column. It is also noted that there are no lysine residues within the HIV GAGp6 late domain. Regardless, there is simply no suggestion in Ott that ubiquitin interacts with HIV GAGp6 late domain. Thus, the rejections under Ott should be withdrawn.

Claim Rejections under 35 USC § 103(a):

Claims 9-11, 16, 21, and 23 stand rejected under 35 USC § 103(a) as being unpatentable over the above discussed Ott in view of Desai *et al., Proc. Natl. Acad. Sci. U.S.A.* 83:8380-8384 (1986) (herein after "Desai").

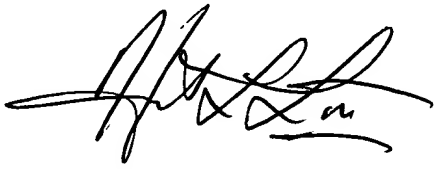
As explained above, Ott discloses that ubiquitin covalently binds to HIV GAGp6 presumably through a lysine residue. It is noted that ubiquitin does not qualify as a "homologue" as defined in the claim limitations. Even assuming ubiquitin is a homologue of Tsg101, Ott does not teach or suggest that ubiquitin interacts with HIV GAGp6 late domain. Nor does Ott teach or suggest that HIV gag p6 binds to Tsg101 or Tsg101 fragments. Desai was cited merely as disclosing HIV GAG and does not add significantly to Ott. Thus, Ott and Desai, each alone, or in combination, do not teach or suggest the claims as amended. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

Applicants believe that once the amendments proposed above have been incorporated into the pending claims, and the arguments presented above addressing the objections and rejections of the Office Action are considered, the objections and rejections will be withdrawn and the pending claims will be in condition for allowance. Consequently, Applicants respectfully request that a timely Notice of Allowance be issued in this case. In order to expedite allowance of this application, the Examiner is invited to telephone the undersigned on his direct office line at 801-883-3463.

A petition for a two-month extension of time for response to an Office Action on the merits is being filed concurrently with this Response. A petition fee of $420, as required under 37 CFR § 1.17(a)(2), is therefore due with this response. The Commissioner is hereby authorized to charge this fee, and any other deficiency, or to credit any over payment, to Deposit Account no. **50-1627**.

Respectfully submitted,



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8-6-04
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